Tissue Repair: Regeneration, Healing and Fibrosis
Wound Healing

Patrice F. Spitalnik, MD
pfs2101@columbia.edu

Learning Objectives

• Differentiate regeneration from repair by fibrosis
• Understand multiple factors and different cell types in the stages of wound healing.
• Know difference between healing by first and second intention
• Understand factors that influence outcome of wound healing and repair.
Growth Factors

- Vascular Endothelial growth factor (**VEGF**) – increased vascular permeability
- Transforming Growth Factor-Beta (**TGF-B**)
- Platelet Derived Growth Factor (**PDGF**)
- Epidermal Growth Factor (**EGF**)
- Fibroblast Growth Factor (**FGF**)
TGF- beta

• Produced by:
  – Platelets and macrophages
  **MOST IMPORTANT FACTOR IN WOUND HEALING**
• Actions:
  – Monocyte chemotaxis
  – Fibroblast migration and proliferation
  – Angiogenesis and fibronectin synthesis
  – Collagen and ECM:
    • Increased synthesis
    • Decreased degradation by MMP’s, increased TIMP’s

Growth Factors and Wound Healing

• **VEGF** and **FGF** - produced by macrophages and increases angiogenesis
• **PDGF** – produced by platelets, is mitogenic for fibroblasts and increases collagen
• **EGF** – produced by macrophages, is mitogenic for keratinocytes and macrophages - **GRANULATION TISSUE**
FGF stimulates keratinocyte migration, wound contracture and matrix deposition
Model of Leukocyte Transmigration
Macrophages in inflammation and repair

- Blood
- Fluid and proteins
- Lymph
- Necrotic tissue
- Neutrophil
- Neutrophil apoptosis
- Macrophage
- Macrophage maturation
- Macrophage growth factors
- New blood vessels
- Repair
- Fibroblasts

Activated macrophage

**TISSUE INJURY**
- Toxic oxygen metabolites
- Proteases
- Neutrophil chemotactic factors
- Coagulation factors
- A.A. metabolites
- Nitric oxide

**FIBROSIS**
- Growth factors (PDGF, FGF, TGFβ)
- Fibrogenic cytokines
- Angiogenesis factors (FGF)
- "Remodeling" collagenases

Figure 3-28. Macrophage products involved in tissue destruction and fibrosis.
Healing is an Outcome for:

- Acute Inflammation
- Chronic Inflammation
- Ischemic Necrosis
- Skin Wounds
- Bone Fractures
Possible outcomes after injury

Regeneration

- If the connective tissue framework is intact
- If the cells are not post-mitotic
- THEN:
  - Complete restoration of the structure and function of the tissue is possible
Chronic Peptic Ulcer

Fibrosis below the ulcer bed
Macrophages in healing and fibrosis

PERSISTENT STIMULUS (chronic inflammation)

Activation of macrophages and lymphocytes

- Growth factors (PDGF, FGF, TGFβ)
  - Proliferation of fibroblasts, endothelial cells, and specialized fibrogenic cells

- Cytokines (TNF, IL-1, IL-4, IL-13)
  - Increased collagen synthesis

- Decreased metalloproteinase activity
  - Decreased collagen degradation

FIBROSIS

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Scar Formation

• If there is substantial damage with loss of the basement membrane or connective tissue framework then:
• Fibrosis or a scar results

Repair by Fibrosis

• Angiogenesis
• Migration and proliferation of fibroblasts
• Deposition of extracellular matrix
• Organization of collagen “remodeling”
• Fibrosis – scar formation
Scarring in the Liver

- Healing by fibrosis after inflammation
- TGF beta implicated in excessive collagen formation
Angiogenesis

- Proteolysis of vessel basement membrane
- Endothelial cell migration and proliferation
- Pericyte recruitment

Growth factor receptors in angiogenesis
Two types of angiogenesis

A. Angiogenesis by mobilization of EPCs from the bone marrow

B. Angiogenesis from pre-existing vessels

ECM and Tissue Remodeling

- Outcome of repair: balance between synthesis and degradation of matrix
- MMP’s are synthesized by fibroblasts, macrophages, neutrophils, epithelial cells, etc destroy matrix (inactive form) activated by proteases and plasmin and inhibited by TIMP’s-synthesized by mesenchymal cells
Overview of Cutaneous Wound Healing

- A defect in the skin occurs
- Fibrin fills in defect – scab forms
- Epithelial regeneration beneath scab
- Granulation tissue – angiogenesis
- Wound contraction
- Collagen remodeling
Cell Migrations in Wound Healing

- **Platelets** form a blood clot and secrete fibronectin (FN) and TGF-beta
- **Macrophages** move in as part of granulation tissue and secrete fibronectin
- **Keratinocytes** or other epithelial cells detach from the basement membrane at wound edge and migrate on fibronectin rich matrix across wound to fill in defect (cells switch receptors from those for BM to FN receptors)
Healing by Primary Intention

- Surgical incision
- Edges easily joined together
- Small amount of granulation tissue
- Little fibrosis
- Wound strength 70-80% of normal by 3 months
Healing by Second Intention

- Large wound, may be infected
- Edges not brought close together
- Large amount of granulation tissue
- Scar formation and contracture
Inhibition of Repair

- Infection with inadequate nutrition (Vitamin C is essential for collagen)
- Glucocorticoids inhibit inflammation with decreased wound strength and less fibrosis.
- Poor perfusion due to diabetes or atherosclerosis.
- Foreign bodies left in the wound.
- Chronic inflammation leads to excess, disabling fibrosis as in rheumatoid arthritis, pulmonary fibrosis and cirrhosis.

Diabetic Foot Ulcer
Case #1

- A 52 year old woman has had fairly well controlled type 2 diabetes mellitus for the past 20 years.
- In the last three months, she has noticed a non-healing ulcer on her heel.
- She asks you what can be done to make it heal better.
Diabetic Foot Ulcer
Case #2

• This is a 63 year old male with Type 2 diabetes mellitus for the past 10 years.
• He requires insulin.
• He presents to you with the complaint of a painless sore on the sole of his foot directly beneath a metatarsal head.
• He asks why his foot has difficulty healing.
Abnormal Repair Processes

- Inadequate scar formation - dehiscence, ulceration
- Excessive scar formation – keloids
- Contracture – exaggeration of normal process (soles, palms, thorax) especially with serious burns
Strategies for Modulating Wound Healing

**Stimulators:**
- Increase epithelial migration
- Increase wound strength, collagen synthesis, TGF-beta
- PDGF used to accelerate healing with chronic pressure sores and diabetic ulcers
- FGF used with success for chronic pressure sores

**Modulators:**
- Delay collagen synthesis (keloids)
- Prevent wound contracture (burns)

Concluding Points

Minor damage acute inflammation (neutrophils), granulation tissue (macrophages, ECM production, angiogenesis) and **healing** (tissue regeneration).

Extensive damage acute and chronic inflammation, large granulation tissue, fibrosis, and scarring. **DO NOT CONFUSE GRANULATION TISSUE WITH GRANULOMA**

- granulation tissue - normal healing
- granuloma - chronic inflammation in some intracellular infections, TB, foreign body reactions, sarcoid, or some fungal infections.